

07-03-2003

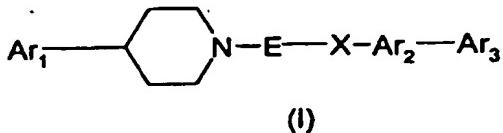
PF4877 - 3 September 2004 PCT/EP03/07612

1

Claims

1. A compound of formula (I), physiologically acceptable prodrugs, salts or solvates thereof;

5



wherein

Ar₁ is:

- (i) phenyl, naphthyl or phenyl fused by a C₃₋₈cycloalkyl; or
- 10 (ii) heterocycl selected from the list consisting of: monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated or aromatic, provided that at least one ring is aromatic;
- 15 where Ar₁ is optionally substituted by 1-4 R¹ groups which may be the same or different;

Ar₂ is a phenyl group, a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, each of which is optionally substituted by 1-4 groups independently selected from the list: C₁₋₄alkyl, halogen, hydroxy, C₁₋₄alkoxy, C₁₋₆acyl, C₁₋₆acyloxy, amino, C₁₋₄alkylamino, di-C₁₋₄alkylamino, -(CH₂)_nOH, -(CH₂)_nNR_xR_y, -O(CH₂)_nO(CH₂)_mOR^a, -O(CH₂)_nC(O)NR_xR_y, -O(CH₂)_nCN, C₂₋₅alkenyl, -O(CH₂)_nCO₂R^a, -OSO₂(CH₂)_pCH₃, -OSO₂NR_xR_y and -CO₂(CH₂)_pCH₃;

20

Ar₃ is:

- (i) phenyl, naphthyl or phenyl fused by a C₃₋₈cycloalkyl; or
- (ii) heterocycl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be

25

07-09-2004

EP0307612

PF4877 - 3 September 2004 PCT/EP03/07612

2

independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

wherein Ar₃ is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy,

5 C₂₋₄alkenyl, C₂₋₄alkenyloxy, C₁₋₄perfluoroalkoxy, C₁₋₄alkylsulfonylamino (such as -NHSO₂CH₃, -NHSO₂CH(CH₃)₂), fluoroC₁₋₄alkylsulfonylamino (such as -NHSO₂CH₂CF₃), C₁₋₄alkylcarbonylamino, fluoroC₁₋₄alkylcarbonylamino, halogen (such as chlorine), nitrile, nitro, C₁₋₄perfluoroalkyl, C₁₋₄alkylcarbonyl, fluoroC₁₋₄alkylcarbonyl, C₁₋₄alkoxycarbonyl, aminocarbonyl, C₁₋₄alkylaminocarbonyl, di-C₁₋₄alkylaminocarbonyl, C₁₋₄alkylsulfonyl, C₁₋₄alkylaminosulfonyl, di-C₁₋₄alkylaminosulfonyl, C₁₋₄alkylsulfonyl and C₁₋₄alkylsulfoxyl;

E is n-butylene;

X is -CONR^a- or -NR^aCO- (where the left hand side of the linkage is attached 15 to E);

wherein

R¹ is halogen, C₁₋₄alkoxy or C₁₋₄alkyl;

R^a is C₁₋₄alkyl or hydrogen;

R_x and R_y are independently hydrogen, C₁₋₄alkyl, hydroxy or C₁₋₄alkoxy,

20 where R_x and R_y are not both hydroxy or both C₁₋₄alkoxy; or R_x and R_y together with the nitrogen to which they are attached form a

5-membered ring which ring is optionally substituted by

-O(CH₂)_nC(O)NR_xR_y, -O(CH₂)_nCN, -O(CH₂)_nO(CH₂)_mOR^a,

-O(CH₂)_nCO₂R^a, -OSO₂NR_xR_y, -OSO₂(CH₂)_pCH₃, -(CH₂)_nC(O)NR_xR_y,

25 -(CH₂)_nCN, -(CH₂)_nO(CH₂)_mOR^a, -(CH₂)_nCO₂R^a, -(CH₂)_nC(O)R^a,

-SO₂NR_xR_y, -SO₂(CH₂)_pCH₃, -CH=CHC(O)NR_xR_y, -CH=CHCN,

-CH=CHCO₂R^a, -CO₂R^a, -C(O)R^a, -C(O)NR_xR_y and C₂₋₅alkenyl;

n and m are independently 1-4; and

p is 0-4.

30

2. A compound according to claim 1 wherein Ar₁ is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indolyl, benzofuranyl, benzothiophenyl or indazolyl.
3. A compound according to claim 2 wherein Ar₁ is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl.

AMENDED SHEET

4. A compound according to any preceding claim wherein X is $-NR^3CO-$.
5. A compound according to any preceding claim wherein Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl.
- 5
6. A compound according to claim 5 wherein Ar_2 is optionally substituted by one or two substituents independently selected from the list: C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, amino C_{1-4} alkyl, mono- C_{1-4} alkylamino C_{1-4} alkyl, di- C_{1-4} alkylamino C_{1-4} alkyl, $-O(CH_2)_nC(O)NR_xR_y$ (where R_x and R_y are independently hydrogen or C_{1-4} alkyl and n is 1-3) or $-CO_2(CH_2)_pCH_3$ (where p is 0-3).
- 10
7. compound according to any preceding claim wherein Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl.
- 15
8. A compound according to claim 7 wherein Ar_3 is substituted by C_{1-4} alkylsulfonylamino, fluoro C_{1-4} alkylsulfonylamino, C_{1-4} alkylcarbonylamino, fluoro C_{1-4} alkylcarbonylamino, halogen, nitrile, C_{1-4} perfluoroalkyl, C_{1-4} alkylcarbonyl, fluoro C_{1-4} alkylcarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl or di- C_{1-4} alkylaminocarbonyl.
- 20
9. A compound according to claim 1 wherein Ar_1 is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indolyl, benzofuranyl, benzothiophenyl or indazolyl; where Ar_1 is optionally substituted by 1-4 R^1 groups which may be the same or different;
- 25
 Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, amino C_{1-4} alkyl, mono- C_{1-4} alkylamino C_{1-4} alkyl, di- C_{1-4} alkylamino C_{1-4} alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;
- 30
 Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4} alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$, fluoro C_{1-4} alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4} alkylcarbonylamino, fluoro C_{1-4} alkylcarbonylamino, halogen (such as chlorine), nitrile,
- 35

AMENDED SHEET

C_{1-4} perfluoroalkyl, C_{1-4} alkylcarbonyl, fluoro C_{1-4} alkylcarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl and di- C_{1-4} alkylaminocarbonyl;

E is n-butylene;

X is $-NR^aCO-$;

5 R¹ is halogen, C_{1-4} alkoxy or C_{1-4} alkyl;

R^a is C_{1-4} alkyl or hydrogen;

R_x and R_y are independently hydrogen or C_{1-4} alkyl;

n is 1-3; and

p is 0-3.

10

10. A compound according to claim 1 wherein

Ar₁ is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar₁ is optionally substituted by 1-2 R¹ groups which may be the same or different;

15

Ar₂ is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4} alkyl, halogen, hydroxy, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, amino C_{1-4} alkyl, mono- C_{1-4} alkylamino C_{1-4} alkyl, di- C_{1-4} alkylamino C_{1-4} alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

20

Ar₃ is phenyl, pyridyl, pyridazinyl, pyrimidinyl or thieryl; wherein Ar₃ is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4} alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$, fluoro C_{1-4} alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4} alkylcarbonylamino, fluoro C_{1-4} alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4} perfluoroalkyl, C_{1-4} alkylcarbonyl, fluoro C_{1-4} alkylcarbonyl, aminocarbonyl, C_{1-4} alkylaminocarbonyl and di- C_{1-4} alkylaminocarbonyl;

25

E is n-butylene;

X is $-NHCO-$;

R¹ is C_{1-4} alkoxy or C_{1-4} alkyl;

30

R_x and R_y are independently hydrogen or C_{1-4} alkyl;

n is 1-3; and

p is 0-3.

11. A compound according to claim 1 wherein

35 Ar₁ is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar₁ is substituted by 1-2 R¹ groups which may be the same or different;

AMENDED SHEET

Ar₂ is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: hydroxy, hydroxyC₁₋₄alkyl, aminoC₁₋₄alkyl, mono-C₁₋₄alkylaminoC₁₋₄alkyl, di-C₁₋₄alkylaminoC₁₋₄alkyl, -O(CH₂)_nC(O)NR_xR_y, and -CO₂(CH₂)_pCH₃;

5 Ar₃ is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar₃ is optionally substituted by 1-4 groups independently selected from the group consisting of: C₁₋₄alkylsulfonylamino (such as -NHSO₂CH₃, -NHSO₂CH(CH₃)₂, fluoroC₁₋₄alkylsulfonylamino (such as -NHSO₂CH₂CF₃), C₁₋₄alkylcarbonylamino, fluoroC₁₋₄alkylcarbonylamino, halogen (such as chlorine), nitrile, C₁₋₄perfluoroalkyl, C₁₋₄alkylcarbonyl, fluoroC₁₋₄alkylcarbonyl, aminocarbonyl, C₁₋₄alkylaminocarbonyl and di-C₁₋₄alkylaminocarbonyl);

10 E is n-butylene;

15 X is -NHCO-;

R¹ is C₁₋₄alkoxy or C₁₋₄alkyl;

R_x and R_y are independently hydrogen or C₁₋₄alkyl;

n is 1-3; and

p is 0-3.

20

12. A compound according to claim 1 wherein

Ar₁ is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar₁ is optionally substituted by 1-2 R¹ groups which may be the same or different;

25 Ar₂ is pyridyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list:

C₁₋₄alkyl, halogen, hydroxy, C₁₋₄alkoxy, hydroxyC₁₋₄alkyl,

aminoC₁₋₄alkyl, mono-C₁₋₄alkylaminoC₁₋₄alkyl, di-

C₁₋₄alkylaminoC₁₋₄alkyl, -O(CH₂)_nC(O)NR_xR_y and -CO₂(CH₂)_pCH₃;

30

Ar₃ is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar₃ is optionally substituted by 1-4 groups independently selected from the group consisting of: C₁₋₄alkylsulfonylamino (such as -NHSO₂CH₃,

-NHSO₂CH(CH₃)₂, fluoroC₁₋₄alkylsulfonylamino (such as

-NHSO₂CH₂CF₃), C₁₋₄alkylcarbonylamino,

fluoroC₁₋₄alkylcarbonylamino, halogen (such as chlorine), nitrile,

35

C₁₋₄perfluoroalkyl, C₁₋₄alkylcarbonyl, fluoroC₁₋₄alkylcarbonyl,

aminocarbonyl, C₁₋₄alkylaminocarbonyl and di-C₁₋₄alkylaminocarbonyl;

AMENDED SHEET

07-09-2004

EP0307612

PF4877 - 3 September 2004 PCT/EP03/07612

E is n-butylene;

X is $-\text{NHCO}-$;

R¹ is C₁₋₄alkoxy or C₁₋₄alkyl;

R_x and R_y are independently hydrogen or C₁₋₄alkyl;

5 n is 1-3; and

p is 0-3.

13. A compound according to claim 1 wherein

Ar₁ is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar₁ is optionally substituted by 1-2 R¹ groups which may be the same or different;

10 Ar₂ is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C₁₋₄alkyl, halogen, hydroxy, C₁₋₄alkoxy, hydroxyC₁₋₄alkyl, aminoC₁₋₄alkyl, mono-C₁₋₄alkylaminoC₁₋₄alkyl, di-

15 C₁₋₄alkylaminoC₁₋₄alkyl, $-\text{O}(\text{CH}_2)_n\text{C}(\text{O})\text{NR}_x\text{R}_y$ and $-\text{CO}_2(\text{CH}_2)_p\text{CH}_3$;

Ar₃ is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thieryl; wherein Ar₃ is optionally substituted by 1-4 groups independently selected from the group consisting of: C₁₋₄alkylsulfonylamino (such as $-\text{NHSO}_2\text{CH}_3$,

- $\text{NHSO}_2\text{CH}(\text{CH}_3)_2$, fluoroC₁₋₄alkylsulfonylamino (such as

20 - $\text{NHSO}_2\text{CH}_2\text{CF}_3$), C₁₋₄alkylcarbonylamino,

fluoroC₁₋₄alkylcarbonylamino, halogen (such as chlorine), nitrile,

C₁₋₄perfluoroalkyl, C₁₋₄alkylcarbonyl, fluoroC₁₋₄alkylcarbonyl,

aminocarbonyl, C₁₋₄alkylaminocarbonyl and di-C₁₋₄alkylaminocarbonyl;

25 E is n-butylene;

X is $-\text{NHCO}-$;

R¹ is C₁₋₄alkoxy or C₁₋₄alkyl;

R_x and R_y are independently hydrogen or C₁₋₄alkyl;

n is 1-3; and

p is 0-3.

30

14. A compound according to claim 1 wherein

Ar₁ is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar₁ is optionally substituted by 1-2 R¹ groups which may be the same or different;

Ar₂ is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which

35 is optionally substituted by 1-4 groups independently selected from the list: C₁₋₄alkyl, halogen, hydroxy, C₁₋₄alkoxy, hydroxyC₁₋₄alkyl,

AMENDED SHEET

aminoC₁₋₄alkyl, mono-C₁₋₄alkylaminoC₁₋₄alkyl, di-C₁₋₄alkylaminoC₁₋₄alkyl, -O(CH₂)_nC(O)NR_xR_y and -CO₂(CH₂)_pCH₃;

Ar₃ is pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar₃ is optionally substituted by 1-4 groups independently selected from the group consisting of: C₁₋₄alkylsulfonylamino (such as -NHSO₂CH₃, -NHSO₂CH(CH₃)₂, fluoroC₁₋₄alkylsulfonylamino (such as -NHSO₂CH₂CF₃), C₁₋₄alkylcarbonylamino, fluoroC₁₋₄alkylcarbonylamino, C₁₋₄alkylcarbonyl, fluoroC₁₋₄alkylcarbonyl, aminocarbonyl, C₁₋₄alkylaminocarbonyl and di-C₁₋₄alkylaminocarbonyl;

5 E is n-butylene;

X is -NHCO-;

R¹ is C₁₋₄alkoxy or C₁₋₄alkyl;

R_x and R_y are independently hydrogen or C₁₋₄alkyl;

15 n is 1-3; and

p is 0-3.

15. A compound according to claim 1 selected from the list:

20 2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1H-indol-3-yl)-piperidin-1-yl]-butyl}-amide (Example 1);

25 2-(4-Cyano-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 7);

30 2-(4-Chloro-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 10);

35 5-(4-Cyano-phenyl)-2-(2-hydroxy-ethyl)-2H-pyrazole-3-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 21);

4-(5-Chloro-thiophen-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 23);

4-(5-Chloro-pyridin-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 32);

4-(6-Chloro-pyridin-3-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 34);

AMENDED SHEET

PCT 34 AMDT

07-09-2004

EP0307612

PF4877 - 3 September 2004 PCT/EP03/07612

8

6-(4-Chloro-phenyl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-
piperidin-1-yl]-butyl}-nicotinamide (Example 38);

6-(4-Cyano-phenyl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-
piperidin-1-yl]-butyl}-nicotinamide (Example 39);

5 6-(5-Chloro-thiophen-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-
2-yl)-piperidin-1-yl]-butyl}-nicotinamide (Example 40); and
2-(4-chlorophenyl)-1,4-dimethyl-1H-imidazole-5-carboxylic acid {4-[4-(1-
methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-
amide (Example 45).

10

16. A pharmaceutical composition comprising a compound as defined in any
preceding claim and a pharmaceutically acceptable carrier or diluent.

15 17. The use of a compound defined in any one of claims 1 to 15 in the manufacture
of a medicament for use in the treatment of conditions resulting from elevated
circulating levels of LDL-cholesterol.

18. A compound defined in any one of claims 1 to 15 for use as a medicament.

AMENDED SHEET